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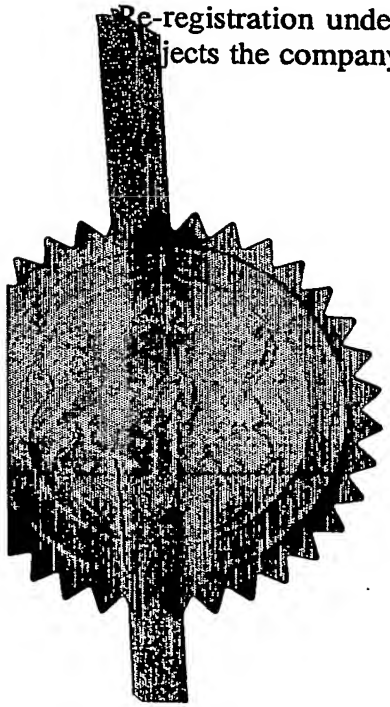

Signed P. Mahoney

Dated 24 July 2003

Patents Form 1/77

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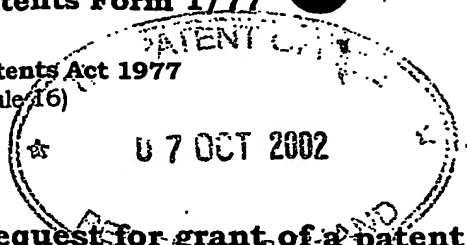

The **Patent Office**

1/77

07OCT02 E746846-2 D00524
P01/7700 0.00-0223224.7

Request for grant of a patent

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The Patent Office
Cardiff Road
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1.	Your reference	4-32716P1	
2.	Patent application number *(The Patent Office will fill in this part)*	07 OCT 2002	0223224.7
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)* 07125487005 Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND SWITZERLAND	
4.	Title of invention	Organic compounds	
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH 1800001 ✓	

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

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Continuation sheets of this form	
Description	11
Claim(s)	4
Abstract	
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co.

Date: 07 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. E. Cheetham**
020 8560 5847

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DUPLICATE

Organic Compounds

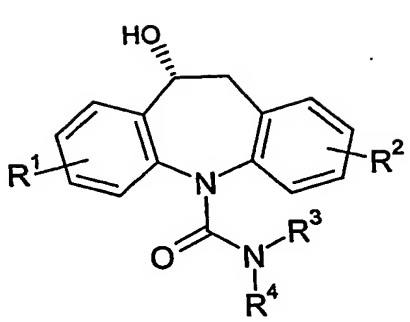
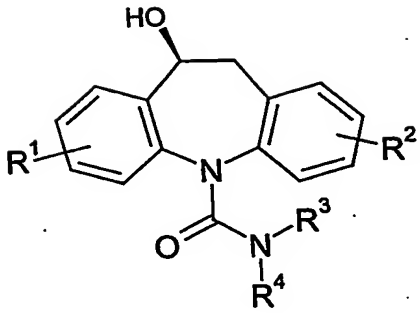
The invention relates to a novel process for the manufacture of substituted enantiopure 10-hydroxy-dihydrodibenz/b,f/azepines by transfer hydrogenation of 10-oxo-dihydrodibenzo/b,f/azepines and to novel catalysts.

Substituted dihydrodibenz/b,f/azepines are understood to be those active agents which may be preferably used to prevent and treat some central and peripheric nervous system disorders. These compounds are well known and some of them have been used widely for the treatment of some pathological states in humans. For example, 5H-dibenz/b,f/azepine-5-carboxamide (carbamazepine) has become established as an effective agent in the management of epilepsy. An analogue of carbamazepine, 10,11-dihydro-10-oxo-5H-dibenzo/b,f/azepine-5-carbamide (oxcarbazepine, see e.g. German Patent 2.011.087) exhibits comparable antiepileptical activity with less side effects than carbamazepine. Oxcarbazepine is metabolized in mammals to 10,11-dihydro-10-hydroxy-5H-dibenzo/b,f/azepine-5-carboxamide (see e.g. Belgian Patent 747.086).

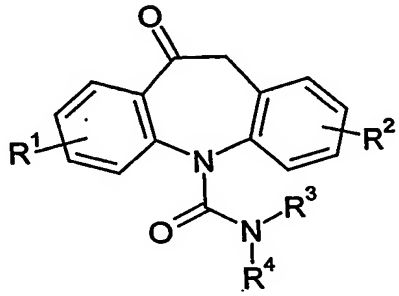
The objective of the present invention is to provide an enantioselective synthesis of substituted 10-hydroxy-dihydrodibenzo/b,f/azepines resulting in high yields and moreover guaranteeing a minimization of the ecological pollution of the environment, being economically attractive, e.g. by using less reaction steps in the reaction sequence for the manufacture of 10,11-dihydro-10-hydroxy-5H-dibenzo/b,f/azepine-5-carboxamide, and leading to largely enantiomerically pure target products and to products that are possible to crystallize. Furthermore, another objective of the present invention is to provide a process that can be carried out in a larger scale and can thus be used as production process.

Surprisingly, the process of the present invention clearly meets the above objectives.

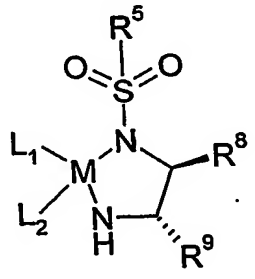
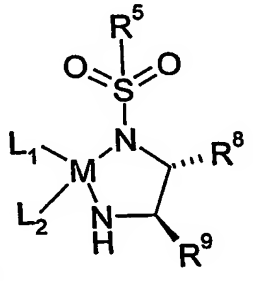
Accordingly the present invention provides a process for the production of a compound of formula Ia or Ib

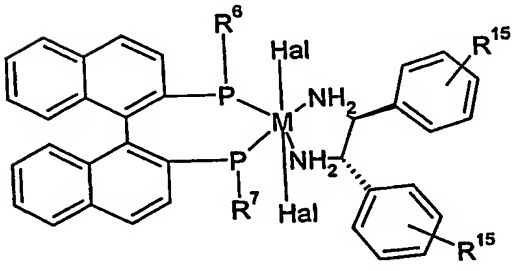
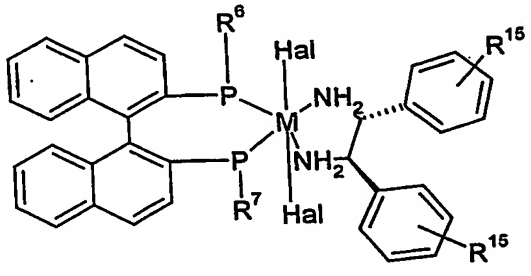

(Ia),

(Ib)

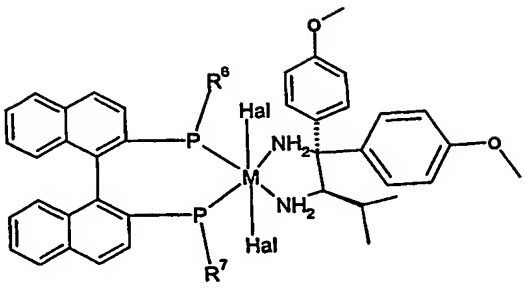
wherein each of R^1 and R^2, independently, are hydrogen, halogen, amino or nitro; and each of R^3 and R^4, independently, are hydrogen or C_1-C_6alkyl; which process comprises the step of reducing a compound of formula II


(II)

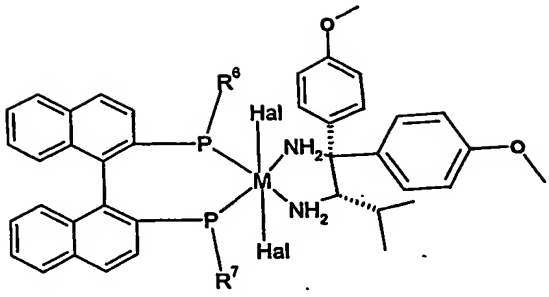
wherein R^1, R^2, R^3 and R^4 are as defined above; in the presence of a hydrogen donor and a reducing agent selected from the group consisting of a compound of formula (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb), (VIa) or (VIb)


(IIIa),

(IIIb),

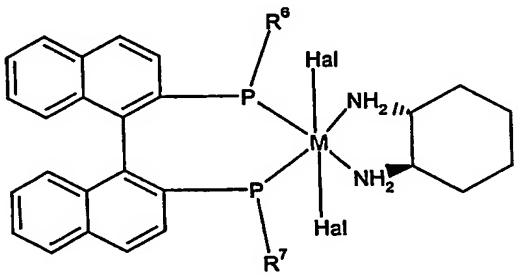

(IVa),

(IVb),



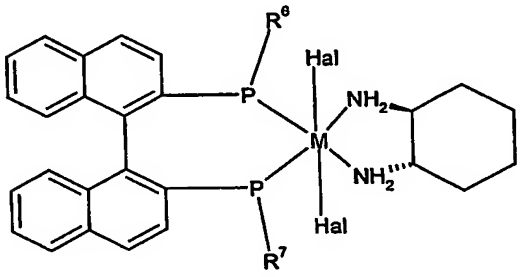
(Va),



(Vb),



(VIa),



(VIb)

wherein

M is Ru, Rh, Ir, Fe, Co or Ni;

L_1 is hydrogen;

L_2 represents an aryl or aryl-aliphatic residue;

Hal is halogen;

R^5 is an aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aryl or aryl-aliphatic residue, which, in each case, may be linked to a polymer;

each of R^6 and R^7, independently, is an aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aryl or aryl-aliphatic residue;

each of R^8 and R^9 is phenyl or R^8 and R^9 form together with the carbon atom to which they are attached a cyclohexane or cyclopentane ring; and

R^{15} is H, halogen, amino, nitro or C_1-C_6alkoxy.

Any aromatic residue of a compound of formula (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb), (VIa) or (VIb) is unsubstituted or substituted. For compounds of formula (IVa), (IVb), (Va), (Vb), (VIa) or (VIb), there are combinations with (R)- or (S)-BINAP possible.

An aliphatic hydrocarbon residue is, for example, C_1-C_7alkyl, C_2-C_7alkenyl or secondarily C_2-C_7alkynyl. C_2-C_7Alkenyl is in particular C_3-C_7alkenyl and is, for example, 2-propenyl or 1-, 2-

or 3-butenyl. C_3-C_5alkenyl is preferred. C_2-C_7-Alkynyl is in particular C_3-C_7alkynyl and is preferably propargyl.

A cycloaliphatic residue is, for example, a C_3-C_8cycloalkyl or, secondarily, C_3-C_8cycloalkenyl. C_3-C_8Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred. C_3-C_8Cycloalkenyl is in particular C_3-C_7cycloalkenyl and is preferably cyclopent-2-en-yl and cyclopent-3-enyl, or cyclohex-2-en-yl and cyclohex-3-en-yl.

A cycloaliphatic-aliphatic residue is, for example, C_3-C_8cycloalkyl-C_1-C_7alkyl, preferably C_3-C_8-cycloalkyl-C_1-C_4alkyl. Preferred is cyclopropylmethyl.

An aryl residue is, for example, a carbocyclic or heterocyclic aromatic residue, in particular phenyl or in particular an appropriate 5- or 6-membered and mono or multicyclic residue which has up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom. Appropriate 5-membered heteroaryl residues are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered residues are in particular pyridyl. Appropriate multicyclic residues are anthracenyl, phenanthryl, benzo[1,3]-dioxole or pyrenyl. An aryl residue may be mono-substituted by e.g. NH_2, OH, SO_3H, CHO, or di-substituted by OH or CHO and SO_3H.

An aryl-aliphatic residue is in particular phenyl-C_1-C_7alkyl, also phenyl-C_2-C_7alkenyl or phenyl-C_2-C_7alkynyl.

Any aromatic residue is preferably unsubstituted. It may also be substituted, for example, by one or more, e.g. two or three, residues e.g. those selected from the group consisting of C_1-C_7alkyl, hydroxy, -O-CH_2-O-, CHO, C_1-C_7alkoxy, C_2-C_8alkanoyl-oxy, halogen, e.g. Cl or F, nitro, cyano, and CF_3.

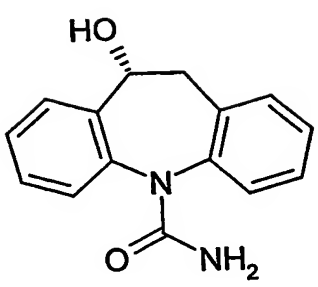
Halogen represents fluorine, chlorine, bromine or iodine.

Polymers may be polystyrene (PS), cross-linked PS (J), polyethylene glycol (PEG) or a silica gel residue (Si). Examples are NH-R^{15} wherein R^{15} is C(O)$(CH_2)_n$-PS or C(O)NH$(CH_2)_n$-PS; and -O-Si$(R^{14})_2(CH_2)_nR^{16}$ wherein n is 1 to 7, R^{14} is C_1-C_6alkyl, e.g. ethyl, and R^{16} is a PS, J, PEG or Si (obtainable by Aldrich, Switzerland).

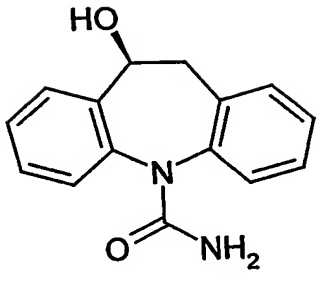
In formula (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb), (VIa) or (VIb) the following significances are preferred independently, collectively or in any combination or sub-combination:
M is Ru, Rh, Ir, preferably Ru.
L_2 is isopropylmethylbenzene, benzene, hexamethylbenzene, mesitylene, preferred is isopropylmethylbenzene.
R^5 is 2- or 3- or 4-pyridyl, 4-chloro-4-phenoxy-phenyl, 4-phenoxy-phenyl, 5-di(m)ethylamino-1-naphthyl, 5-nitro-1-naphthyl, 2-, 3-, 4-nitrophenyl, 4-vinylphenyl, 4-biphenylyl, 9-anthracenyl, 2,3 or 4 hydroxyphenyl, tolyl, phenanthryl, benzo[1,3]-dioxole, dimethyl(naphthalene-1-yl)-amine, mono to tristrifluoromethylphenyl, chrysenyl, perylenyl or pyrenyl.
Each of R^6 and R^7, independently, are phenyl, 4-methylphenyl or 3,5-dimethylphenyl, preferred is phenyl.
Each of R^8 and R^9 is phenyl or cyclohexyl or substituted phenyl, preferably is phenyl.
Preferred Hal is chloro.
Preferred R^{15} is H.
L_1 is as defined above.

A preferred hydrogen donor is, for example, a system comprising 2-propanol, 3-pentanol, or most preferably HOOCH in the presence of an amine, such as triethylamine, DBU or other tertiary amines. The hydrogen donor may also be used as inert solvent, especially 2-propanol and most preferably HCOOH. An alternative hydrogen donor is 2-propanol in the presence of various catalysts and base, e.g. Ru[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-*p*-cymene) and base or „in situ" [Ru(η^6-*p*-cymene)Cl_2]$_2$ with chiral ligand (*R*,*R*- or *S*,*S*-TsDPEN, amino-alcohol) and base. The preferred bases are: *t*-BuOK, KOH or *i*-PrOK.

In a preferred aspect, the invention provides a process for the production of a compound of formula I'a or I'b

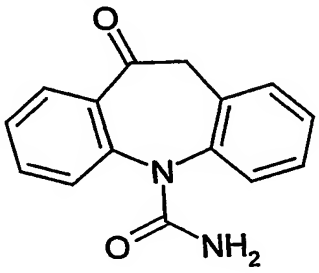


(I'a),



(I'b)

which process comprises the step of reducing the compound of formula II'

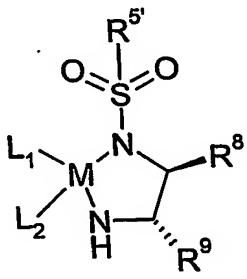


(II')

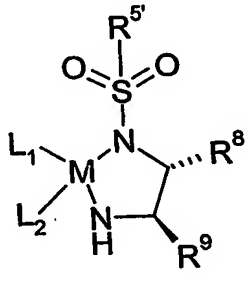
in the presence of a reducing agent selected from the group consisting of a compound of formula (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb), (VIa) or (VIb) as described above and a hydrogen donor.

The compounds of formula II and II' are known and may be prepared as described in WO-A2-0156992.

The invention further provides the novel compounds of formula III'a and III'b

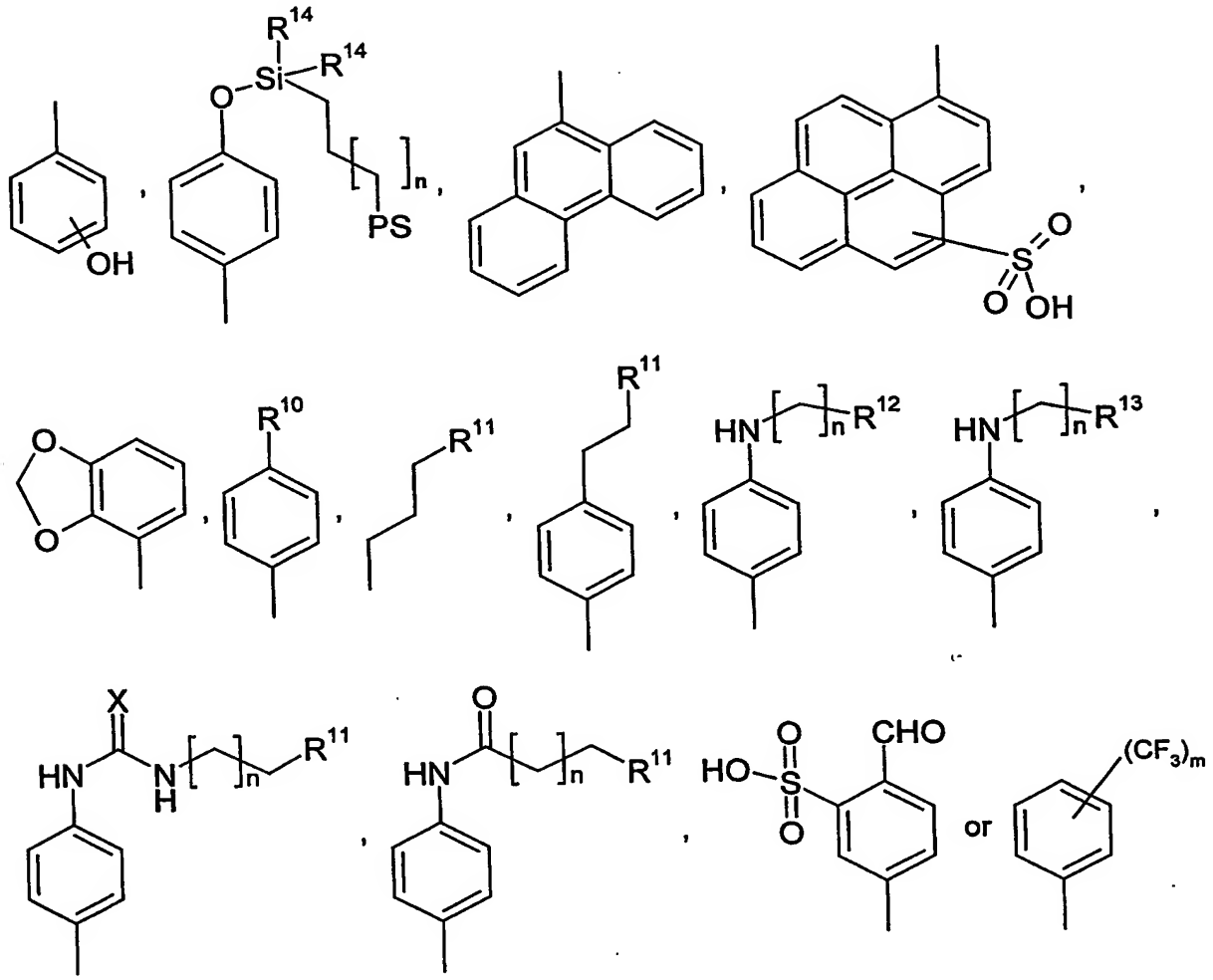


(III'a),



(III'b)

wherein M, L_1, L_2, R^8 and R^9 are as defined above and $R^{5'}$ is a group of formula



wherein

n is 0, 1, 2, 3, 4, 5, 6 or 7;

X is O or S;

R^{10} is polystyrol;

R^{11} is silica gel;

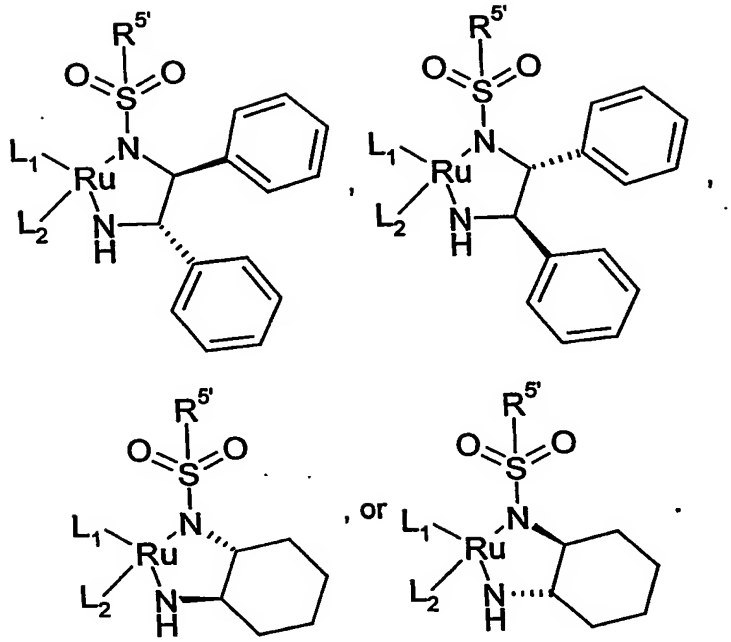
R^{12} is cross-linked polystyrol;

R^{13} is polyethylene-glycol;

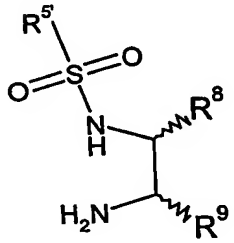
R^{14} is C_1-C_6alkyl; and

m is 1, 2 or 3.

The following compounds of formula (III'a) or (III'b) wherein L_1, L_2 and $R^{5'}$ are as defined above, are preferred:



Compounds of formula (III'a) or (III'b) may be prepared by reacting a compound of formula VII



(VII),

wherein $R^{5'}$, R^8 and R^9 are as defined above, with $[MCl_2(p\text{-cymene})]_2$ in conventional manner, e.g. as described for M = Ru in the Example 3.

Some compounds of formula (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb), (VIa) or (VIb) are known and may be prepared as described in Haack et al., Angew. Chem., Int. Ed. Engl. 1997, 36, 285-288.

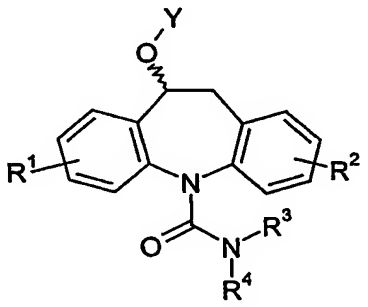
The hydrogenation described above may be carried out, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to

about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

The hydrogenation may be carried out in a suitable inert solvent, such as an ether, e.g. tetrahydrofuran, an ester, such as ethylacetate, a halogenated solvent, such as methylenchloride, supercritical CO_2, ionic liquids, a nitrile, especially acetonitrile, an amide, such as dimethylformamide or dimethylacetamide and in a temperature range from, for example, from -78°C, to the boiling point of the solvent, preferably at room temperature, e.g. as described in the Examples.

It is known from the art that asymmetric transfer hydrogenation using a Ru (II) catalyst (esp. a Noyori catalyst) is carried out in the absence of water and under inert gas conditions. Surprisingly, the transfer hydrogenation step according to the present invention can be run in a water containing solvent system and in the absence of an inert gas. This means that the reaction is successful even though the solvent used comprised water (3 % by Karl-Fischer titration).

Optionally, the compounds of formula (I) may be converted into their corresponding pro-drug esters of formula (VIII)



(VIII)

wherein

Y is hydrogen, unbranched or branched C_1-C_{18}alkylcarbonyl, aminoC_1-C_{18}alkylcarbonyl, C_3-C_8cycloalkylcarbonyl, C_3-C_8cycloalkylC_1-C_{18}alkylcarbonyl, halogenC_1-C_{18}alkylcarbonyl, unsubstituted or at the aryl substituted C_5-C_{10}arylC_1-C_{18}alkylcarbonyl, unsubstituted or at the heteroaryl substituted C_5-C_{10}heteroarylC_1-C_{18}alkylcarbonyl, C_1-C_{18}alkoxycarbonyl; and and R^1, R^2, R^3 and R^4 are as described above (see also EP-B1-751129 for production conditions).

The following examples illustrate the invention.

Example 1: Procedure for the enantioselective Transfer Hydrogenation of 10-Oxo-10,11-dihydro-dibenzo[*b,f*]azepine-5-carboxylic acid amide to *R*(-)-10,11-Dihydro-10-hydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide:

To a mixture of 10-Oxo-10,11-dihydro-dibenzo[*b,f*]azepine-5-carboxylic acid amide (300 mg, 1.189 mmol) and RuCl[(1*R*,2*R*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene, Aldrich, Switzerland) (8.8 mg, 0.0138 mmol) in CH_2Cl_2 (15 ml) is added dropwise a premixed solution of formic acid and NEt_3 (5:2, 328 mg:289 mg) at 23 °C and stirred for 10 min. The clear solution is heated to reflux for 16 h. The reaction mixture is cooled to room temperature (RT), diluted with CH_2Cl_2 (20 ml) and neutralised with aqu. $NaHCO_3$. After washing with brine the solution is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using a 6:1 EtOAc-MeOH mixture as eluent to afford of *R*(-)-10,11-Dihydro-10-hydroxy-5*H*-dibenzo[*b,f*]azepine-5-carboxamide (enantiomeric purity (ee) > 99 % determined by HPLC on Chiracel OD, Retention time: 9.46 min. $[\alpha]_D^{rt}$ = -195.3 ° (ethanol). ^{1}H-NMR (400 MHz, $CDCl_3$):7.70-7.20 (m, 8 H), 5.30 (br s,1 H), 5.10-4.60 (br s, 2 H), 3.75-3.40 (m, 1 H), 3.20-2.90 (m, 1 H), 2.50 (br s, 2 H). NMR-Datas refer to Lit.: Benes, J et al., *J. Med. Chem.* **1999**, *42*, 2582-2587. Molecular weight: 254.291

Example 2: Procedure for the enantioselective Transfer Hydrogenation of 10-Oxo-10,11-dihydro-dibenzo[*b,f*]azepine-5-carboxylic acid amide to *S*(+)-10,11-Dihydro-10-hydroxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide:

To a mixture of 10-Oxo-10,11-dihydro-dibenzo[*b,f*]azepine-5-carboxylic acid amide (300 mg, 1.189 mmol) and RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene) (11 mg, 0.0173 mmol) in CH_2Cl_2 (15 ml) is added in two portions a premixed solution of formic acid and NEt_3 (5:2, 656 mg:578 mg) at 23 °C and stirred for 10 min. After that formic acid is added (50 µl) and the clear solution is heated to reflux for 16 h. The reaction mixture is cooled to RT, diluted with CH_2Cl_2 (20 ml) and neutralised with aqu. $NaHCO_3$. After washing with brine the solution is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using a 6:1 EtOAc-MeOH mixture as eluent to afford of *S*(+)-10,11-Dihydro-10-hydroxy-5*H*-dibenzo[*b,f*]azepine-5-carboxamide (ee > 99 % by HPLC on Chiracel OD). Retention time: 12.00 min. $[\alpha]_D^{rt}$ = +196.6 ° (ethanol). ^{1}H-NMR (400 MHz, $CDCl_3$):7.70-7.20 (m, 8 H), 5.30 (br s,1 H), 5.10-4.60 (br s, 2 H), 3.75-3.40 (m, 1 H), 3.20-2.90 (m, 1 H), 2.50 (br s, 2 H). NMR-Datas refer to Lit.: Benes, J et al., *J. Med. Chem.* **1999**, *42*, 2582-2587. Molecular weight: 254.291

Alternative production: To a mixture of 10-Oxo-10,11-dihydro-dibenzo[*b*,*f*]azepine-5-carboxylic acid amide (300 mg, 1.189 mmol) and RuCl[(1*S*,2*S*)-*p*-dansylNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene) (8.5 mg, 0.012 mmol) in CH_2Cl_2 (15 ml) is added dropwise a premixed solution of formic acid and NEt_3 (5:2, 328 mg:289 mg) at 23 °C and stirred for 10 min. The clear solution is heated to reflux for 16 h. The reaction mixture is cooled to RT, diluted with CH_2Cl_2 (20 ml) and neutralised with aqu. $NaHCO_3$. After washing with brine the solution is concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel using a 6:1 EtOAc-MeOH mixture as eluent to afford of *S*(+)-10,11-Dihydro-10-hydroxy-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide.

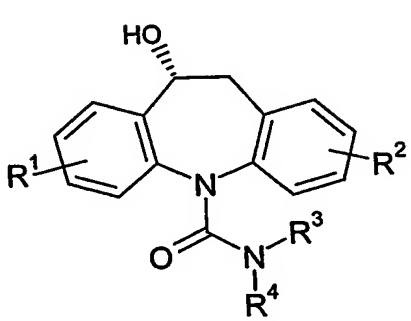
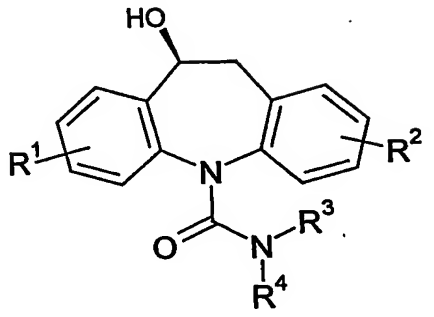
Example 3: Preparation of RuCl[(1*S*,2*S*)-*p*-dansylNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-*p*-cymene)

a) Preparation of (S,S)-5-dimethylamino-naphthalene-1-sulfonic acid (2-amino-1,2-diphenyl-ethyl)-amide: To a solution of (*S*,*S*)-diphenylethylenediamine (250 mg, 1.2 mmol) and triethylamine (0.5 ml) in THF is added dropwise a solution of dansyl chloride (318 mg, 1.2 mmol) in THF (2 ml) at 0°C. After stirring 16 h at RT the solvent is removed in vacuum and the residue is resolved in methylenchloride (20 ml). The organic solution is washed with $NaHCO_3$ solution (5 ml), dried over Na_2SO_4 and after filtration the solvent is removed. Flash chromatographie afford (*S*,*S*)-5-dimethylamino-naphthalene-1-sulfonic acid (2-amino-1,2-diphenyl-ethyl)-amide as yellow oil which crystallizes by drying in vacuum. M: 445.59. ^{1}H-NMR (400 MHz, $CDCl_3$):8.36 (t, *J* = 7.5 Hz, 2 H), 8.17 (dd, *J* = 7.2, 1.2 Hz, 1 H), 7.47 (dd, *J* = 8.8 Hz, 1 H), 7.34 (dd, *J* = 8.5 Hz, 1 H), 7.24-7.16 (m, 4 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 6.99-6.74 (m, 6 H), 4.61 (d, *J* = 8.5 Hz, 1 H), 4.20 (d, *J* = 8.5 Hz, 1 H), 2.80 (s, 6 H).

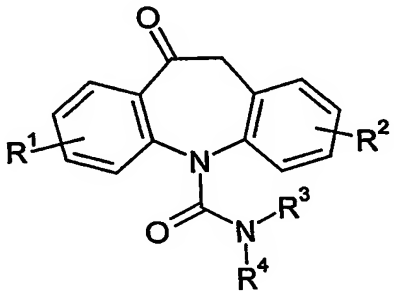
b) Preparation of RuCl[(1S,2S)-p-dansylNCH(C_6H_5)CH(C_6H_5)NH_2](η^6-p-cymene): A solution of (*S*,*S*)-5-dimethylamino-naphthalene-1-sulfonic acid (2-amino-1,2-diphenyl-ethyl)-amide (80mg, 0.18 mmol), NEt_3 (36 mg, 0.36 mmol) and [$RuCl_2$(p-cymene)]$_2$ (55 mg, 0.09mmol) in 2-propanol is heated at 80°C for 1 h. The solvent is removed after that und the dark red residue is washed with water (2 ml). The solid is dried in vacuum and used without any purification. M: 715.34.

Claims:

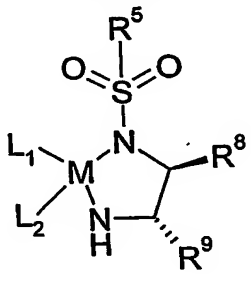
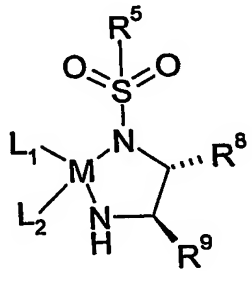
1. A process for the production of a compound of formula Ia or Ib

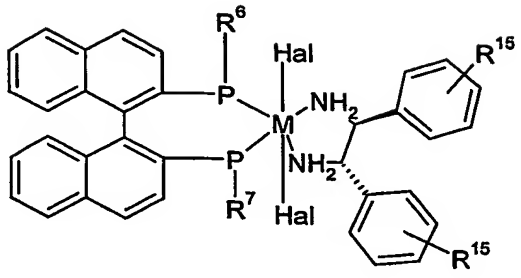

(Ia),

(Ib)

wherein each of R^1 and R^2, independently, are hydrogen, halogen, amino or nitro; and each of R^3 and R^4, independently, are hydrogen or C_1-C_6alkyl; which process comprises the step of reducing a compound of formula II

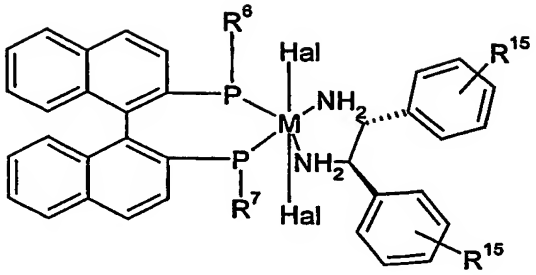

(II)

wherein R^1, R^2, R^3 and R^4 are as defined above; in the presence of a hydrogen donor and a reducing agent selected from the group consisting of a compound of formula (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb), (VIa) or (VIb)

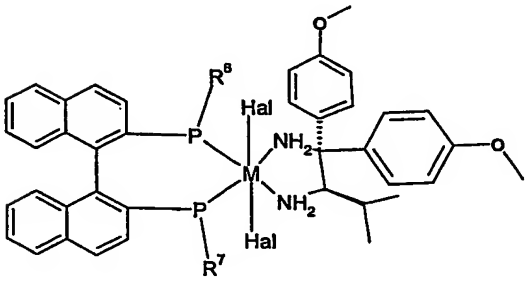

(IIIa),

(IIIb),



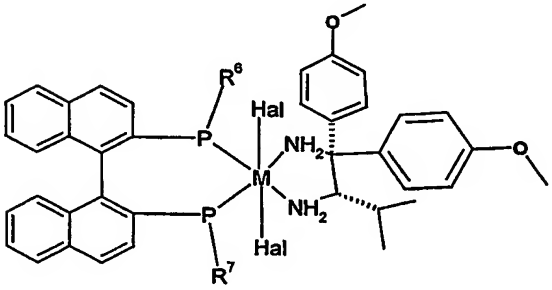
(IVa),



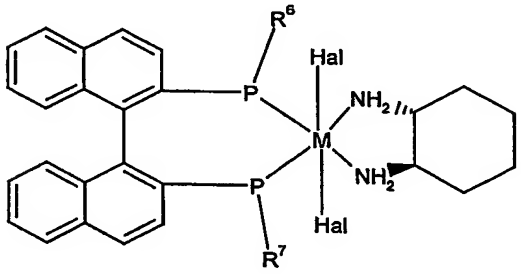
(IVb),



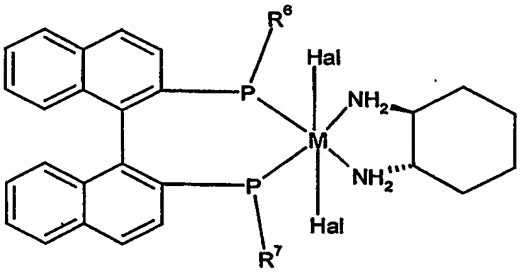
(Va),



(Vb),



(VIa),



(VIb)

wherein

M is Ru, Rh, Ir, Fe, Co or Ni;

L_1 is hydrogen;

L_2 represents an aryl or aryl-aliphatic residue;

Hal is halogen;

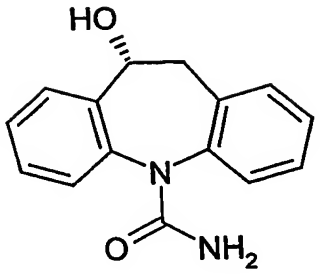
R^5 is an aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aryl or aryl-aliphatic residue, which, in each case, may be linked to a polymer;

each of R^6 and R^7, independently, is an aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aryl or aryl-aliphatic residue;

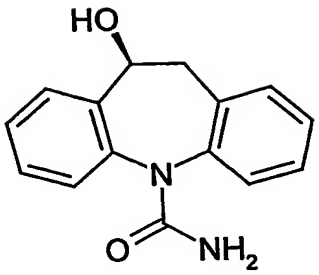
each of R^8 and R^9 is phenyl or R^8 and R^9 form together with the carbon atom to which they are attached a cyclohexyen or cyclopenten ring; and

R^{15} is H, alkyl, halogen, amino, dialkylamino, nitro or C_1-C_6alkoxy.

2. The process according to claim 1 for the production of a compound of formula I'a and I'b



(I'a),

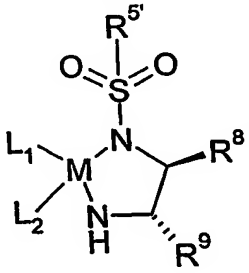


(I'b).

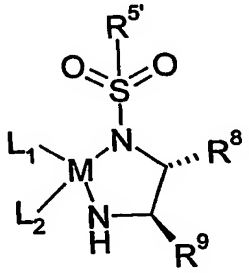
3. The process according to claim 1 whereas the transfer hydrogenation step takes place in a water containing solvent system.

4. The process according to claim 3 whereas the transfer hydrogenation step takes place in the absence of an inert gas.

5. A compound of formula III'a and III'b

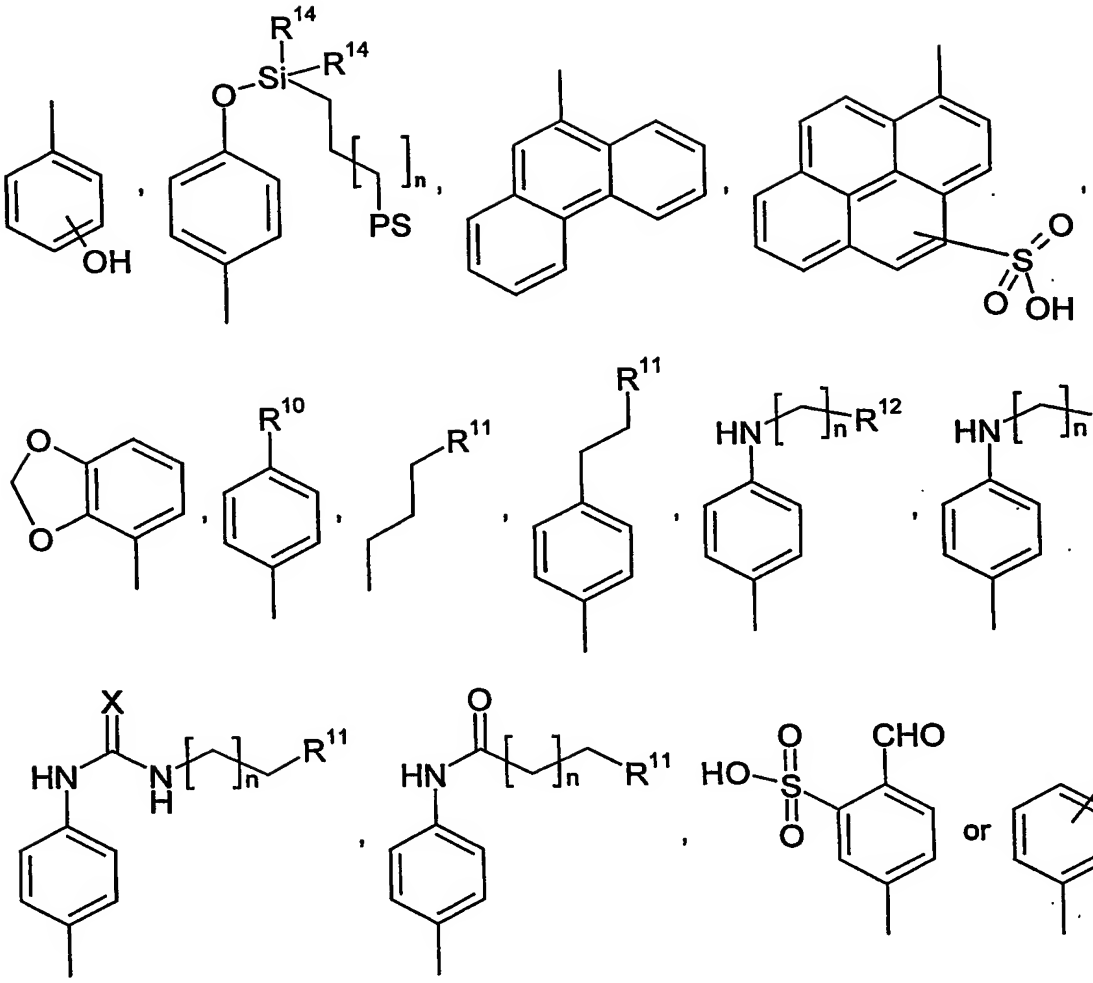


(III'a),



(III'b)

wherein M, L_1, L_2, R^8 and R^9 are as defined above and $R^{5'}$ is a group of formula



wherein

n is 0, 1, 2, 3, 4, 5, 6 or 7;

X is O or S;

R^{10} is polystyrol;

R^{11} is silica gel;

R^{12} is cross-linked polystyrol;

R^{13} is polyethylene-glycol;

R^{14} is C_1-C_6alkyl; and

m is 1, 2 or 3.

PCT Application
EP0311034

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